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Digitization of multistep organic synthesis in reactionware for on-demand pharmaceuticals

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Abstract

Chemical manufacturing is often done at large facilities that require a sizable capital investment and then produce key compounds for a finite period. We present an approach to the manufacturing of fine chemicals and pharmaceuticals in a self-contained plastic reactionware device. The device was designed and constructed by using a chemical to computer-automated design (ChemCAD) approach that enables the translation of traditional bench-scale synthesis into a platform-independent digital code. This in turn guides production of a three-dimensional printed device that encloses the entire synthetic route internally via simple operations. We demonstrate the approach for the g-aminobutyric acid receptor agonist, (\pm)-baclofen, establishing a concept that paves the way for the local manufacture of drugs outside of specialist facilities.

The manufacture of active pharmaceutical ingredients (APIs) is vital for modern health care, yet critical drugs are regularly manufactured for a finite period in a limited number of sites. The manufacture of chemical products—whether bulk, fine, or specialty chemicals, such as APIs—is currently based on a model whereby a central plant is exclusively designed for the manufacture of the product, or range of products, sold by that particular company (**1**). This model holds whether the manufacturer is a large pharmaceutical company or, as is increasingly the case, a contract research organization operating large chemical manufacturing plants to order from the pharmaceutical industry. This process leads to safety issues around both the storage and transport of such materials, as well as the issues inherent in the large-scale manufacture of chemicals (**2**). In addition, these large-scale plants are often at the mercy of complicated and global supply chains of raw materials, the failure of which at any point will reduce or halt the capacity of the plant to produce materials and deliver them effectively (**3, 4**). Also, when a given complex intermediate or API goes out of production, the plants are often repurposed and the manufacturing capacity is lost. The reinstatement of the process would require, in the best case, substantial capital investment to reconfigure a chemical plant for its synthesis. To alleviate this issue, we propose a concept whereby the large-scale manufacturing process of complex fine chemicals, such as APIs, is augmented by distributed, point-of-use manufacturing in self-contained cartridges, requiring limited user interaction to produce the desired products on demand. To achieve this, we developed a methodology for the translation of bench-scale synthesis procedures into a step-by-step workflow that could be used to create digital designs for custom reactionware that can be fabricated by using three-dimensional (3D) printing technologies. In this way, we aim to move beyond the preserve of industrial manufacturing and prototyping applications (**5**), to revolutionize the relationship between the design, manufacture, and operation of functional devices (**6–11**) and exploit the increasing use of 3D printing in the automation of the chemical sciences (**12–15**). This methodology, which is in stark contrast to both large- and medium-scale traditional chemical manufacture, and also to the use of continuous-flow and microreactor approaches (**1, 16, 17**), allows for the distribution of simple chemical precursors and solvents rather than the complex products themselves. These precursors could then continue to benefit from the economies of scale brought by traditional manufacturing processes while complex products with short shelf lives, or lower and more distributed demand, can be produced locally. This has added benefits in terms of manufacture of the final products as the synthesis of smaller quantities is inherently safer than large-scale processes and poses less risk to both operators and infrastructure. Further, the translation of these synthetic approaches into a digitally defined format, where the reactor design and, eventually, an automated synthesis procedure are encoded, could allow the digitization of all chemical products into a very low-cost manufacturing format. This could allow large numbers of discontinued APIs to be made available as they can be brought back into production on a small scale by the fabrication and use of the appropriate cartridges (**18, 19**).

As a proof of principle, we present a process by which the traditional laboratory-scale synthesis of a commercially available API can be translated into the design of an integrated cartridge. To do this, all the reaction steps and intrasynthesis purification processes are encoded into the 3D architecture of the cartridge so that the chemical reactions, work-ups, and purification are done with minimal user intervention and exposure automatically. We have demonstrated this process in the full synthesis of the anticonvulsant medication (\pm)-baclofen (see below).

This method for translating traditional laboratory syntheses into a form that can be encapsulated in a single cartridge is split into three layers of consideration, which were iteratively reevaluated during the cartridge development process. The first is the “conceptual layer,” where the chemical reactions and processes necessary are identified and developed. The second is the “digital layer,” in which

these processes are translated into digital 3D models of the final cartridge devices. Finally, a “physical layer,” where the digital models are realized as either a modular implementation or a monolithic implementation, is used to generate the finalized cartridge, which can be used to effect the designed synthesis (**Fig. 1**). These physical systems can then be tested for efficacy as a final implementation, before iterating the process to develop reliable cartridge syntheses.

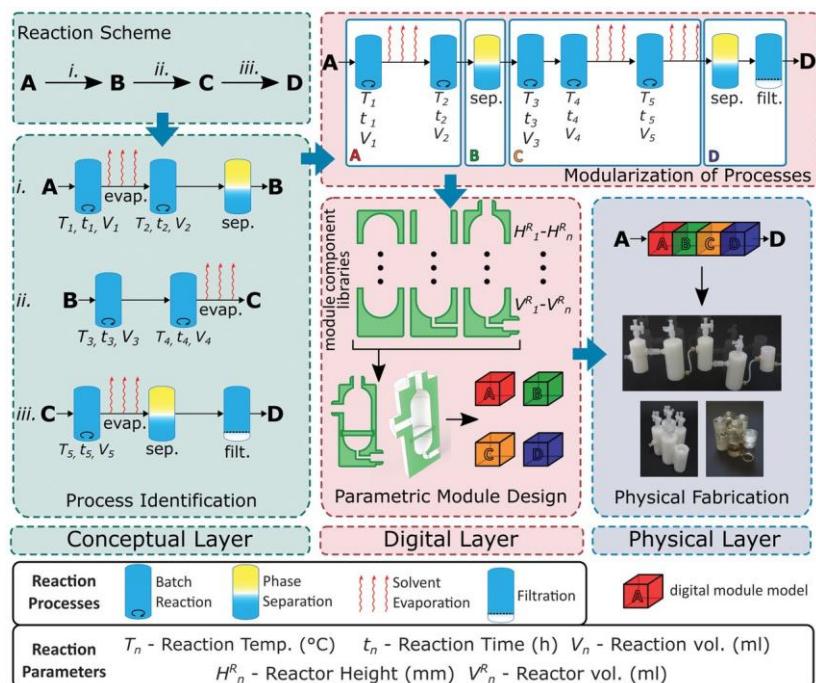


Figure 1- Schematic representation of the translation of a multistep synthesis from conception through to implementation as a reaction cartridge.

Reactions necessary for the synthesis are identified ($A \rightarrow B \rightarrow C \rightarrow D$, top left panel) and the specific chemical and physical processes and reaction parameters necessary for each reaction are laid out (conditions i. – iii., left panel). These processes are then translated into bespoke reaction modules designed to accomplish one or more of the chemical processes identified in the previous step (top right panel). The modules are then designed as 3D CAD models (lower center panel), with libraries of module components to accommodate the required reaction parameters. These digital models can then be fabricated to produce either a modular or monolithic implementation (lower right panel) of the process.

First, the fundamental chemistry required for the transformations is considered and optimized to minimize the necessary interstep purification for the completion of the full synthesis. This approach is similar to that taken to develop telescoped (i.e., consecutive transformations in a single reactor or sequence of reactors without isolation and purification of intermediates) and “one-pot” syntheses (**20, 21**), often used in process chemistry, both of which aim to maximize the efficiency of the synthetic route. Although here it is not necessary to produce genuinely telescoped syntheses, as modules for interstep purification can be built into the cartridge design, the synthesis of the desired compound, including all reagents and starting materials for all the necessary steps, must be considered as a unified process. The choice of synthetic route to any target compound will be dictated by a number of factors, including the relative availability and cost of starting materials, reagents, and solvents, as well as the compatibility of reaction and purification sequences with the reactor modules produced. In any wide-scale application of our approach, a cost analysis of any proposed synthetic route will have to be performed to ensure its viability for the product. Once the chemistry for the synthesis is developed, a sequence can be produced where the physical processes and reaction parameters—such as heating, cooling, phase separations, reaction volumes, and times—can be identified.

Vital to the success of these modules is the compatibility of the cartridge material with the chemistry being performed. Whereas traditional laboratory syntheses take place mostly in glassware, we use polypropylene (PP) as a basic structural material for the fabrication of the cartridges. We have found that this polyolefinic material, while demonstrating a robust range of chemical compatibility for traditional synthetic organic reactions, is also a suitable substrate for 3D printing applications (**22–24**). This gives the best balance of chemical resistance and material properties for 3D printing. Therefore, the first step in the design process is testing the reactions necessary for compatibility in the reactor materials. Future iterations of the concept could expand on the materials and fabrication processes available for the reaction modules to further develop the range of chemistries feasible in this system, using, for example, perfluorinated polymers to increase the chemical resistance of the module.

To demonstrate the feasibility of incorporating these PP reactors into the production of APIs, we tested a number of reactions that lead to such targets in test modules fabricated from PP (**Fig. 2**). We tested reactions for the synthesis of three APIs: the central nervous system inhibitor (\pm)-baclofen (**25**), the anticonvulsant lamotrigine (**26**), and the gastroprotective agent zolimidine (**27**). As can be seen, all of the reactions tested were observed to work, but with slightly lower efficiency in PP reactors than in traditional glass reactors, owing to physical loss of material on the relatively rough PP surface hampering product recovery. Surface roughness is inherent in the 3D printed process; however, use of other, as yet undeveloped, materials or different manufacturing techniques could reduce this issue. The zolimidine reactions, particularly the copper-catalyzed iodination reaction, experienced a pronounced reduction in efficiency, compared to (\pm)-baclofen or lamotrigine. We surmised that this was due to side reactions of the iodine with the polypropylene. These issues highlight that the process of translation from glassware must take into account both the physical and chemical properties and limitations of the reactor substrate (**23**). For this reason, the first two syntheses were selected for further development into reaction cartridges to explore the concept.

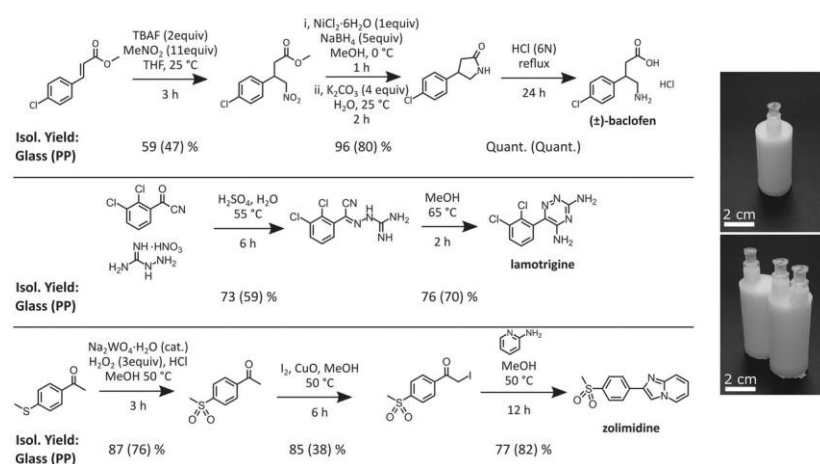


Figure 2- Comparison of glass reactors with plastic reactionware for the optimized synthetic routes to (\pm)-baclofen (top), lamotrigine (middle), and zolimidine (bottom) with reaction yields for each step (reaction yields in PP vessels given in parentheses).

Single (top right) or double (bottom right) chambered polypropylene reaction test cartridges were used. PP, polypropylene; TBAF, tetrabutylammonium fluoride; THF, tetrahydrofuran.

Once the processes needed for the reaction sequence are identified, the combined continuous protocol is mapped onto the 3D digital designs for the target-specific cartridge. The sequence of processes is split into a series of modules, with each representing a telescoped series of processes that can take place in a single chamber of the 3D printed system. Each process module is then

created as a digital model that can be manipulated to provide the correct physical dimensions necessary for the reaction scheme. The 3D models of the cartridges used in this study were created with OpenSCAD software, an open-source framework for CSG (constructive solid geometry) modeling that allows a highly flexible and configurable approach to create versatile libraries of components as reusable pieces of code. Once defined, these pieces of code can be manipulated by the software, allowing the generation of complex reactor geometries with minimal human inputs. For example, in this study, we designed a module library consisting of interchangeable top and bottom components with varying features that can be easily combined to produce reaction vessels with different shapes and features. From a single line of code, an entire module can be created, with 18 different shapes available (i.e., three different tops and six different bottoms can be selected; **Fig. 3**). The modules were designed around simple chambers where each reaction or process could be performed in as close a manner as possible to the way it would be carried out with traditional batch chemical techniques, easing the transition between published synthesis in glassware and “cartridge” synthesis. Typically, a standard module would have an opening on the top of the wall of the chamber for transfer of reaction mixtures from previous modules and an opening at the bottom of the chamber for expelling material from the module subsequent to the completion of the desired process. The transfer of material between modules is facilitated by a further opening in the roof of the compartment, which can be used to apply pressure that forces the reaction medium out of the chamber via the outlet at the bottom. The opening at the top otherwise equalizes pressure throughout the device to prevent the premature transfer of material, and also allows for application of vacuum to remove and exchange solvents. These modules can then be combined in sequences by use of further components of our module library such as siphon tubes for the transfer of material from one reaction module to another.

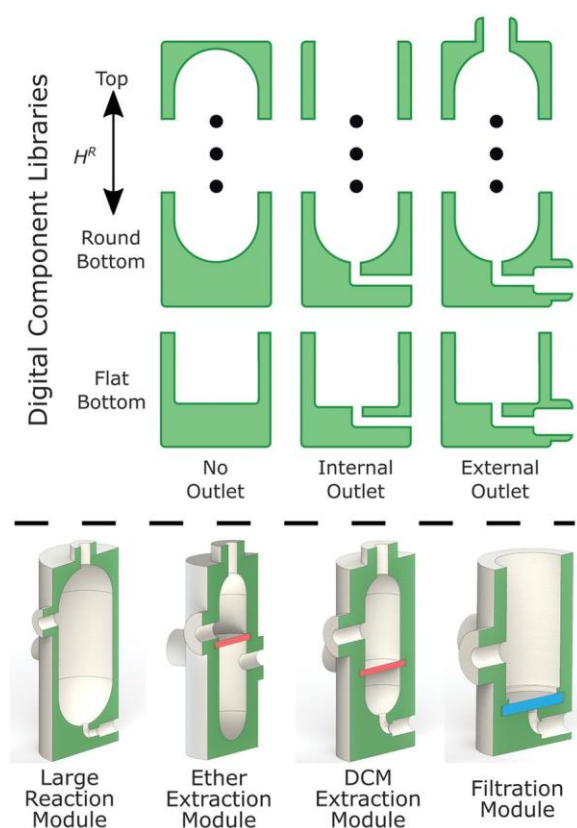


Figure 3- Parameterized approach to the design of individual process modules.

Digital libraries of module components (top) can be easily assembled to produce a wide range of module geometries dictated by the specific process and reaction parameters (e.g., solvent volumes, number of inputs and outputs, etc.) (bottom). Hydrophobic filters for phase separation are shown in red, and fritted glass filters are shown in blue. DCM, dichloromethane. HR, reactor height.

Once a reaction chamber is created, new features can be introduced by subtracting or adding shapes to the module. For example, a filtration device can be made from a module with a top input, a round bottom with a port, and a glass filter. To achieve this feature, a cylindrical model conforming to the dimensions of the physical filter to be inserted is created and subsequently subtracted from the model of a reaction chamber, producing a void space in the model into which the filter fits (see supplementary materials). Phase separation modules were achieved in a similar manner by using hydrophobic frit inserts that effectively separate organic and aqueous phases for product extractions. In keeping with our desire to design synthesis cartridges that can be produced outside traditional manufacturing regimes, we have exploited our group's development of 3D printed reactors—reactionware—for synthetic chemical applications as a method of prototyping the physical reactors (**28, 29**). Three-dimensional printing-based fabrication approaches have the added advantage of being intimately linked to the design process.

Fabrication of the modular system was carried out on low-cost (~\$2000) 3D printers, Ultimaker 2 and 2+, although many other fused deposition modeling (FDM) printers could print the 3D modules produced through this approach. If it is necessary to incorporate nonprinted materials during 3D printing of the final module, a preprogrammed pause in the printing process is instigated at a point just above the designed void, and the component is inserted in this space before the resumption of printing. Upon completion of printing, the inlet and outlet ports were tapped with a ¼ inch unified national fine (UNF) thread to allow ease of integration with the external infrastructure for performing the reaction sequences. Using standard ports allowed us to attach either standard fluidic tubing connectors such as those found in traditional flow synthesis setups, or widely used Luer lock adapters. These Luer lock connectors are easily reconfigurable, facilitating feedback into the design process.

The API chosen to accomplish a complete end-to-end synthesis was the central nervous system depressant and antispastic medication (\pm)-baclofen (**30, 31**) [*RS*- β -(4-chlorophenyl)- γ -aminobutyric acid] (**4**) (**Fig. 4**), a derivative of γ -aminobutyric acid (GABA) that modulates the action of this central inhibitory neurotransmitter (**25**). This target was chosen as an example to demonstrate that even relatively short syntheses require a disproportionately larger set of chemical processing steps to effect the full synthesis; in the future, we envision that the synthesis of larger numbers of compounds and compound classes will greatly expand the scope of this approach. (\pm)-Baclofen has found a number of applications since its first reported synthesis and is currently being investigated beyond its traditional use, as a high-dose treatment for alcoholism (**32**). Many syntheses of (\pm)-baclofen have been published since it was first reported, often proceeding through the formation, and subsequent hydrolysis, of β -(4-chlorophenyl)- γ -butyrolactam (**3**). We have modified such a traditional synthesis of (\pm)-baclofen starting from the commercially available material methyl 4-chloro-cinammate (**1**), and proceeding via the Michael addition of nitromethane to form 4-nitro-3-(4-chlorophenyl)butanoic acid (**2**), followed by nickel-catalyzed reductive lactamization and subsequent acid hydrolysis to produce the final product in its commercially available racemic form as a hydrochloride salt. This three-reaction-step sequence contains 12 individual processing steps that must be incorporated into the reactionware device to complete the synthesis (**Fig. 4**). This sequence was designed to be particularly amenable to translation into the modular or monolithic system as at each stage, the reactions are either sufficiently clean, or reaction impurities that would impinge on subsequent process in the synthesis could be readily removed by phase partition. The final product

is purified through a methanol–diethyl ether crystallization, which yields a crystalline solid that can be retrieved directly from the cartridge device. An animation of the entire process, showing the passage of reagents, processes, and work-ups, is shown in movie S1.

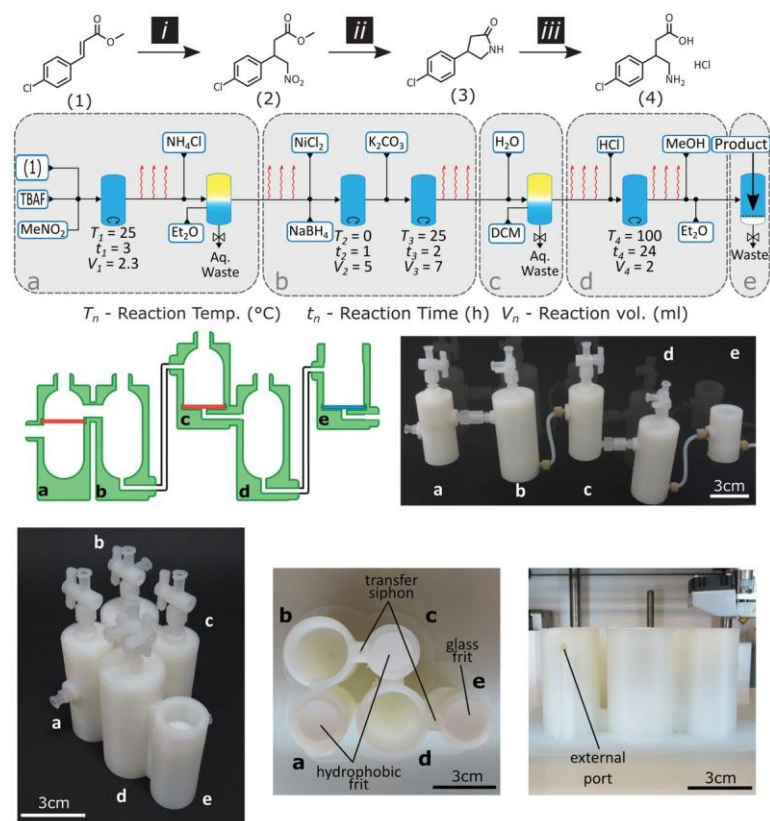


Figure 4- Synthesis of (±)-baclofen in a series reaction cartridges.

(Top) Conceptual synthetic procedure for the synthesis of (±)-baclofen under the conditions described in Fig. 2, showing the necessary processing sequence to effect this synthetic pathway. These processes were then split into modules (a) to (e) (indicated by gray boxes in the process sequences), which we translated into a digital design (middle left) and finally fabricated as either a modular (middle right) or monolithic (bottom left) implementation. A partially fabricated monolithic cartridge is also shown indicating the placement of non-3D printed components and internal fluidic pathways (bottom center and right). Both modular and monolithic cartridges are shown with Luer taper-compatible valving for interfacing with external fluidic inputs and pressure or vacuum lines.

Each of these processes was translated into operations that could be successfully embodied in one or more reaction or purification modules. The specific reaction modules used for the synthesis of (±)-baclofen were (a) a combined Michael addition, evaporation and ether extraction module; (b) a combined solvent exchange and reduction module; (c) a phase separation and filtration module; (d) a combined solvent exchange and hydrolysis module; and (e) a filtration module. Individual modules were fabricated for a “plug-and-play” approach to the reaction process development by using Luer lock fittings to connect individual modules and Luer taper-compatible valves to interface with pressure or vacuum systems. This design allowed testing of each individual process in isolation before the modules were combined to build up the full synthesis. Finally, the module designs were “digitally stitched together” by using the developed CAD libraries for internal fluidic pathways to create the design for a monolithic synthesis cartridge. Once fabricated, the individual modules and the monolithic cartridges were evacuated and filled with a nitrogen atmosphere to ensure an inert environment for the subsequent chemistry.

The first chamber, (a), consists of a lower volume (4.9 ml) where the initial reaction can take place and is separated from the upper outlet by a hydrophobic frit. Reactor modules (b) and (d) consist of a single unbroken reaction chamber (31.8 ml) with sufficient volume to accommodate the reaction volumes and extraction solvents from the previous processes before concentration under reduced pressure. Extraction module (c) consists of a chamber of sufficient volume (4.7 ml) to contain the aqueous phase from the previous chamber, which has a drain at the bottom covered by a hydrophobic frit that prevents both solid material and aqueous solution from passing into the next chamber or module. The final module is a filtration module for separating and retrieving the final product. This single module can be either open to the atmosphere or enclosed as required. During the fabrication process, chambers or modules that required stirring were equipped with a PTFE (polytetrafluoroethylene)-coated magnetic stirring bead (length 10 mm) to enable mixing of the contents. Each module or chamber of the monolith was equipped with a ¼ inch UNF threaded port carrying a female Luer lock adapter, which was used to introduce an inert (dry, N₂) atmosphere, or reduced pressure, into the system. The modular system was designed such that there was a single fluidic path through the reactor; flow from one chamber into the next was induced either by pressure from excess solvent, in the case of the phase separation processes, or the introduction of nitrogen pressure difference between the relevant chambers to push the reaction mixture through an embedded channel running from the bottom of one chamber to the top of the next.

Starting materials were prepared as simple solutions and transferred to the cartridge via standard Luer syringes. The cooling and heating required for the reaction sequence were achieved by the immersion of the reaction cartridge or module in an ice or sand bath, respectively, and the temperature required for the reactions can be achieved automatically on a stirring-hotplate. The exact sequence of operations, positioning of the module in the heating or cooling bath, and time intervals necessary for completing the synthesis are outlined in the supplementary materials (figs. S12 and S13 and table S3).

Performing the synthesis starting from 200 mg of **1** in the manner described yielded 98 mg (39% yield over three reaction steps and 12 processing steps from **1** with ≥95% purity as determined by high-performance liquid chromatography) of (±)-baclofen hydrochloride salt, which is more than 1 day's maximum dosage of the drug. Better efficiency of reaction can be achieved with lower concentrations of starting materials (using a similar cartridge at half concentration, i.e., 100-mg scale, gave a 44% yield over three steps of similar purity). Increasing the volume of the reactor as well increases the quantity of (±)-baclofen obtained [a 300-mg scale synthesis yielded 133 mg (35%) (±)-baclofen]. The integration of the reaction processing steps into the design of the modules greatly simplifies the operations required to perform the reaction sequence compared to traditional bench synthesis and simultaneously reduces the level of technical skills required to perform the process down to simple operations that do not require the specific skills of a trained synthetic chemist. Although the total time for the reaction sequence is around 40 hours in this case, including all intermediate operations, the workflow is constrained by the geometry of the device, so all human interaction is limited to simple interventions at specific time periods, and it should be possible to shorten the interaction time further. The use of such bespoke, single-use cartridges would greatly reduce the time spent on glassware preparation, liquid handling, and other ancillary tasks associated with the majority of chemical syntheses at this scale. Also, by using the geometry of the reactor to constrain the operation of the synthesis, we reduce the human decision making involved in the synthesis processes, making the sequence more reproducible. Given sufficient facilities, several instances of the synthesis cartridge could be used at once, achieving scalability by numbering-up arrays of cartridges, and using these in parallel to increase the output. As a result of the ability to parameterize and encode multistep organic synthesis reactions with work-ups embedded, we

envisage that a digital programmable universal heater-stirrer-solvent-reagent plug-and-play device can be constructed into which only the cartridge, specific to a given synthesis, can be plugged in.

The (±)-baclofen synthesis necessitated liquid handling and separation of reaction chambers to effect the full reaction sequence. In some cases, however, syntheses can be conducted in single reaction cartridges, depending on the nature and quality of the interstep purification required. For example, the synthesis of lamotrigine (**Fig. 2**) can be achieved in a single cartridge as the intermediate material is insoluble in the reaction solvent at low temperatures. In a single, closed, filtration module, the initial reaction product could be washed and processed in situ before introduction of the solvent for the subsequent cyclization step. This stands in contrast to the traditional procedure, which requires the solid product of the first step to be removed from the initial reactor to be filtered, dried, and then reintroduced to a reactor for the second step of the synthesis. Performing the synthesis of lamotrigine on a 250-mg scale of starting material yields 112 mg (46% over two reaction steps) of the final product, giving an off-white crystalline powder.

The digital approach to the design of the system that we have adopted allows the blueprints for these cartridges to be stored electronically for implementation as and when required. The distribution model for fine and specialty chemicals, such as the APIs implied by this approach, would lead to a decentralizing of logistical approaches to chemical manufacture. Here, any location with access to a sufficiently diverse market of chemical precursors and suitable cartridge fabrication facilities could be used to produce chemical products, which could previously be achieved only in a fully equipped synthesis laboratory with highly trained staff. This approach not only holds promise for eventually delivering on-demand personalized medicines manufactured at, or near, the point of use, but also has short-term potential applications in the synthesis of APIs that are currently out of production. An immediate impact of digitization is that the cost for synthesis at the bench scale (milligrams) could decrease markedly owing to savings in labor and infrastructure with only a one-off digitization cost (and allow operators to make 5 to 10 different products at the same time). Once the saving meets the digitization cost, the efforts of the expert chemist will shift from bespoke on-demand chemical manufacturing to chemical digitization (see supplementary materials for an economic analysis). Our methodology will have the most rapid impact for chemicals that are currently produced on demand in small batches and that occupy a gap in the market where the demand for a product is sufficient for it to be commercially viable but insufficient to justify plant-scale production. This gap lies between the high cost of bench-scale versus reactor-scale synthesis, and thus the digitization benefit of compounds in this zone is high.

The regulatory framework necessary to produce complex materials in this fashion will need thorough attention; indeed, our approach would require a completely new system for the regulation of API manufacture. This system would have to be developed alongside the evolution of this approach as a method for pharmaceutical synthesis, which we have presented here in proof-of-concept form; however, we can envision a situation in which regulatory agencies certify specific cartridge or module designs as soon as a digitized process is fully established (including the embedded quality-control protocols), independent of the physical location of person who uses the cartridge. This approach has multiple benefits. First, the framework can adopt well-established methods of digital object certification from the information technology universe (e.g., digital signing with asymmetric ciphers). Second, no explicit certification would be needed for each new “facility” (which might be a hospital or a private house) that would need the drug. Third, existing methods for protecting and manipulating digital content provide much more efficient models for distribution and regulation compared to the retail and patent system, respectively. These regulatory issues surrounding the commercial or clinical application of this approach are not trivial, and care must be

taken to ensure that end-user safety is not compromised. However, we believe that the benefits in terms of efficiency of delivery, robustness of supply, and range of materials available could lead to the digitization of chemical synthesis.

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We acknowledge the help of S. Marshall in compiling our analysis of the economic impact of our methodology. Supplementary materials include a PDF document detailing the materials and methods used in this article; the STL and OpenSCAD files used to generate all 3D printed objects mentioned; a schematic movie illustrating the process of baclofen synthesis in the monolithic cartridge; and Python code that can be used to automate the stirrer-hotplate operations for the baclofen synthesis. We gratefully acknowledge financial support from the Engineering and Physical Sciences Research Council (grant nos. EP/H024107/1, EP/J015156/1, EP/K021966/1, EP/L015668/1, EP/L023652/1) and European Research Council (project 670467 SMART-POM). This research was developed with funding from the Defense Advanced Research Projects Agency (DARPA). The views, opinions and/or findings expressed are those of the author and should not be interpreted as representing the official views or policies of the Department of Defense or the U.S. Government. L.C. is the founder and director of CroninGroupPLC and is listed as an inventor on a patent application filed by The University of Glasgow (GB 1800299.8). L.C. conceived the initial concept and the design approach; P.J.K. designed the reactionware with help from J.P.F. and S.Z.; G.M. and R.C.S. telescoped the methods, porting them from glass to plastic; and P.J.K. developed the monolithic cartridges with help from S.Z. J.S.M. helped evaluate the purity of the products, and P.J.K. coordinated the team with help from L.C.

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